

REMARKS

Applicants submit this Amendment in response to the Office Action of June 19, 2003. The claims have been amended as follows.

Claims 1 to 23 have been canceled. Claims 24, 40, and 41 have been amended to specify that the concentrations called for are % w/w. Claims 45 to 81 have been added. Support for these claims is found in the claims as filed.

OBJECTIONS TO THE CLAIMS

The Examiner has objected to claim 23 as being a duplicate of claim 21. Applicants submit that this objection is moot as both claims 21 and 23 have been canceled in the present Amendment.

REJECTIONS OF THE CLAIMS

I. Rejections under 35 U.S.C. §112, second paragraph.

A. The Examiner has rejected claims 3, 4, 17-19, and 40-44 as being indefinite for the lack of units associated with percentages. Claims 3, 4, 17, and 19 have been canceled. Claims 40-44 have been amended to indicate that the percentage concentrations are w/w. Accordingly, Applicants request the Examiner to withdraw the rejection of these claims on this ground.

B. Applicants submit that the rejections of claims 6, 8, and 20-23 are moot as these claims are canceled in this Amendment.

II. Rejections under 35 U.S.C. §102

A. Struengmann, WO 99/09988

The Examiner has rejected claims 1, 5, 6, 9, 11, and 17 as being anticipated under 35 U.S.C. §102(b) by the disclosure of Struengmann, WO 99/09988. Applicants traverse the rejection of these claims on this ground.

Struengmann discloses, at Example IV/10 on page 18, a solution comprising betacyclodextrin hydrate (BCDx), nicotinamide, and meloxicam. In order to expedite prosecution of the present application, claims 1, 5, 6, 9, 11, and 17 have been canceled. All claims presently in the application call for betacyclodextrin, metronidazole, and niacin or niacinamide (nicotinamide). The subject matter of such claims is not disclosed in Struengmann. Accordingly, Applicants submit that all claims presently in the application distinguish over the disclosure of Struengmann and the Examiner is requested to withdraw this basis of rejection.

B. Chang et al., U.S. Patent No. 6,468,989

The Examiner has rejected claims 1-4 and 9 as being anticipated under 35 U.S.C. §102(e) over the disclosure of Chang, U.S. Patent No. 6,468,989. Applicants traverse the rejection of these claims on this ground.

Chang discloses aqueous compositions containing niacinamide, metronidazole, and hydroxypropyl-betacyclodextrin. As amended, all claims presently in the application call for betacyclodextrin, metronidazole, and niacin or niacinamide (nicotinamide). Accordingly, Applicants submit that all claims presently in the application distinguish over the disclosure of Chang, and the Examiner is requested to withdraw this basis of rejection.

III. Rejections under 35 U.S.C. §103

A. Struengmann, WO 99/09988

The Examiner has rejected claims 1, 5, 6, 9, 11, 15, 17, and 18 under 35 U.S.C. §103(a) as being obvious over Struengmann, WO 99/09988. Applicants traverse the rejection of these claims on this ground.

As discussed above, Struengmann discloses a solution comprising betacyclodextrin hydrate (BCDx), nicotinamide, and meloxicam. Struengmann does not disclose or suggest a solution comprising betacyclodextrin, nicotinamide, and metronidazole, as is presently claimed. Further, Applicants submit that the disclosure of Struengmann does not pertain to a claim calling for specified concentrations of betacyclodextrin or niacinamide, as is called for in claim 17 of the present application, now canceled. Struengmann discloses an improved dissolution rate, which is a concept that is distinct from solubility.

All claims presently in the application call for betacyclodextrin, metronidazole, and niacin or niacinamide (nicotinamide). The subject matter of such claims is not disclosed or suggested in Struengmann. Accordingly, Applicants submit that all claims presently in the application distinguish over the disclosure of Struengmann and the Examiner is requested to withdraw this basis of rejection.

B. Kata, Acta Pharm. Hung, 54:116-122 (1984), and Chien, U.S. Patent No. 4,032,645

The Examiner has rejected claims 1-14, 17, 19-21, 23, 24, 27-29, 31, 32, 40, 41, 43, and 44 as being obvious in view of the combined disclosure of Kata, Acta Pharm. Hung,

54:116-122 (1984), and Chien, U.S. Patent No. 4,032,645. Applicants traverse the rejection of these claims on this ground.

Kata discloses aqueous solutions comprising betacyclodextrin and metronidazole. Kato does not disclose niacinamide. Chien discloses aqueous solutions comprising metronidazole and the combination of N,N-dimethylacetamide, ethanol, an aqueous buffer, and nicotinamide. Chien does not disclose betacyclodextrin.

Applicants submit that the prior art does not disclose or suggest the combination of betacyclodextrin, metronidazole, and nicotinamide (niacinamide) as is presently claimed. Kata does not disclose nicotinamide. Chien discloses aqueous solutions of nicotinamide and metronidazole only in combination with high concentrations of ethanol and N,N-dimethylacetamide.

Applicants submit that there is no suggestion in the prior art to select nicotinamide from the several essential components of the solution of Chien and combine the nicotinamide with the betacyclodextrin of Kata in order to make an aqueous metronidazole solution. Applicants submit that the Examiner has failed to establish a prima facie case of obviousness of the claims over the combined disclosure of Kata and Chien.

Moreover, assuming arguendo that the Examiner has established a prima facie case of obviousness of the claims based on the combined disclosures of Kata and Chien, Applicants have established that the combination of betacyclodextrin and nicotinamide or niacin produces unexpected advantageous properties pertaining to the aqueous solubility of metronidazole. Such unexpected advantageous properties are disclosed in Example 5 of the specification of the present application.

Applicants submit that the present claims, which call for the combination of metronidazole, betacyclodextrin, and niacinamide, patentably distinguish over the prior art and the Examiner is requested to withdraw the rejection of claims 1-14, 17, 19-21, 23, 24, 27-29, 31, 32, 40, 41, 43, and 44 as being obvious in view of the combined disclosure of Kata, Acta Pharm. Hung, 54:116-122 (1984), and Chien, U.S. Patent No. 4,032,645.

C. Kata, Acta Pharm. Hung, 54:116-122 (1984), Chien, U.S. Patent No. 4,032,645, and Czernielewski, U.S. Patent No. 5,849,776

The Examiner has rejected claims 15, 16, 18, 22, 26, 30, 33-39, and 42 as being obvious in view of the combined disclosure of Kata, Acta Pharm. Hung, 54:116-122 (1984), Chien, U.S. Patent No. 4,032,645, and Czernielewski, U.S. Patent No. 5,849,776. Applicants traverse the rejection of these claims on this ground.

The disclosures of Kato and Chien are discussed above. Czernielewski discloses aqueous metronidazole gels for treatment of dermatologic conditions. Czernielewski does not disclose betacyclodextrin, niacinamide, or niacin.

As discussed above, the prior art does not suggest the combination of metronidazole, betacyclodextrin, and either niacinamide or niacin. As discussed above, there is no suggestion in the prior art to select nicotinamide from the disclosure of Chien and combine it with betacyclodextrin and metronidazole in aqueous solution, as is presently claimed. The disclosure of Czernielewski also fails to provide any suggestion to combine betacyclodextrin, metronidazole, and niacin or niacinamide. Accordingly, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness of the present claims.

Moreover, assuming *arguendo* that the Examiner has established a *prima facie* case of obviousness of the claims based on the combined disclosures of Kata, Chien, and Czernielewski, Applicants have established that the combination of betacyclodextrin and nicotinamide or niacin produces unexpected advantageous properties pertaining to the aqueous solubility of metronidazole. Such unexpected advantageous properties are disclosed in Example 5 of the specification of the present application.

Applicants submit that the present claims, which call for the combination of metronidazole, betacyclodextrin, and niacinamide, patentably distinguish over the prior art and the Examiner is requested to withdraw the rejection of claims 15, 16, 18, 22, 26, 30, 33-39, and 42 as being obvious in view of the combined disclosure of Kata, *Acta Pharm. Hung.* 54:116-122 (1984), Chien, U.S. Patent No. 4,032,645, and Czernielewski, U.S. Patent No. 5,849,776.

D. Kata, *Acta Pharm. Hung.* 54:116-122 (1984), Chien, U.S. Patent No. 4,032,645, and Loftsson, U.S. Patent No. 5,324,718

The Examiner has rejected claim 25 as being obvious in view of the combined disclosure of Kata, *Acta Pharm. Hung.* 54:116-122 (1984), Chien, U.S. Patent No. 4,032,645, and Loftsson, U.S. Patent No. 5,324,718. Applicants traverse the rejection of this claim on this ground.

The disclosures of Kato and Chien are discussed above. Loftsson discloses methods for enhancing the solubility enhancing property of a cyclodextrin by combining it with a water-soluble polymer. Such combination may be used to solubilize metronidazole. Loftsson does not disclose niacinamide or niacin.

As discussed above, the prior art does not suggest the combination of metronidazole, betacyclodextrin, and either niacinamide or niacin. As discussed above, there is no suggestion in the prior art to select nicotinamide from the disclosure of Chien and combine it with betacyclodextrin and metronidazole in aqueous solution, as is presently claimed. The disclosure of Loftsson also fails to provide any suggestion to combine betacyclodextrin, metronidazole, and niacin or niacinamide. Loftsson's disclosure is limited to the combination of a cyclodextrin and a polymer. Accordingly, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness of the present claims.

Moreover, assuming *arguendo* that the Examiner has established a prima facie case of obviousness of the claims based on the combined disclosures of Kata, Chien, and Loftsson, Applicants have established that the combination of betacyclodextrin and nicotinamide or niacin produces unexpected advantageous properties pertaining to the aqueous solubility of metronidazole. Such unexpected advantageous properties are disclosed in Example 5 of the specification of the present application.

Applicants submit that the present claims, which call for the combination of metronidazole, betacyclodextrin, and niacinamide, patentably distinguish over the prior art and the Examiner is requested to withdraw the rejection of claim 25 as being obvious in view of the combined disclosure of Kata, *Acta Pharm. Hung.* 54:116-122 (1984), Chien, U.S. Patent No. 4,032,645, and Loftsson, U.S. Patent No. 5,324,718.

IV. REJECTION FOR DOUBLE PATENTING

The Examiner has rejected claims 1-4, 9, and 15 for double patenting over claims 2, 3, and 9 of Chang, U.S. Patent No. 6,468,989. Applicants traverse the rejection of these claims on this ground.

All claims of the Chang patent call for hydroxypropyl-betacyclodextrin. Claims 1-4, 9, and 15 have been canceled. As amended, all claims of the present application call for betacyclodextrin. Applicants submit that the rejection on the ground of double patenting in view of Chang, U.S. Patent No. 6,468,989, has been overcome and the Examiner is requested to withdraw the rejection of the claims on this ground.

CONCLUSION

Applicants submit that, as amended herein, the claims are in condition for allowance and an early notice to that effect is respectfully requested.

Respectfully submitted,



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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Box 1450, Alexandria, VA 22313-1450 on July 28, 2003.

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